

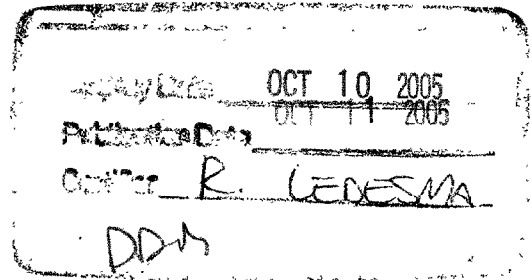
DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 310 and 341

[Docket No. 2004N-0289]

RIN 0910-AF34



**Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Amendment of Final Monograph for Over-the-Counter Nasal Decongestant Drug Products**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Final rule.

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**SUMMARY:** The Food and Drug Administration (FDA) is amending the final monograph (FM) for over-the-counter (OTC) nasal decongestant drug products (drug products used to relieve nasal congestion due to a cold, hay fever, or other upper respiratory allergies) to remove the indication “for the temporary relief of nasal congestion associated with sinusitis” and to prohibit use of the terms “sinusitis” and “associated with sinusitis” elsewhere on the labeling. This final rule is part of FDA’s ongoing review of OTC drug products.

**DATES:** *Effective Date:* This regulation is effective [insert date 18 months after date of publication in the **Federal Register**].

*Compliance Dates:* The compliance date for products with annual sales less than \$25,000 is [insert date 24 months after date of publication in the **Federal Register**]. The compliance date for all other products is [insert date 18 months after date of publication in the **Federal Register**].

**FOR FURTHER INFORMATION CONTACT:** Michael T. Benson, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Silver Spring, MD 20993, 301-796-2090.

**SUPPLEMENTARY INFORMATION:**

**I. Background**

In the **Federal Register** of August 2, 2004 (69 FR 46119), FDA published a proposed rule to amend the FM for OTC nasal decongestant drug products to remove the indication “for the temporary relief of nasal congestion associated with sinusitis” and to prohibit use of the terms “sinusitis” and “associated with sinusitis” elsewhere on the labeling. Recent publications (Refs. 1 and 2) indicate that prospective studies on the role of nasal decongestants in the treatment of sinusitis are lacking, and the data on their use as an adjunct in the treatment of sinusitis are limited and controversial. Despite the lack of evidence for their use, nasal decongestants are recommended or prescribed by health care providers as adjunctive therapy for sinusitis. This treatment occurs within a physician-patient relationship and should not be construed as evidence that consumers should self-diagnose and self-manage sinusitis. In addition, there is preclinical evidence that topical nasal decongestants may have a negative effect on the resolution of sinusitis, as they may increase the degree of sinus inflammation (Ref. 3). Due to the current labeling, FDA is concerned that consumers use OTC nasal decongestant drug products (both oral and topical) to treat symptoms associated with sinusitis, rather than seeking medical evaluation and definitive treatment. The delay in medical evaluation could also result in a lost opportunity for early diagnosis of another serious medical condition in consumers who have symptoms similar to those of sinusitis. Consumers who have bacterial sinusitis

could potentially have their condition worsen by delaying treatment with appropriate antibiotic medications, possibly resulting in serious complications. Consumers who have both sinusitis and accompanying asthma could have complications from both diseases if there is a delay in appropriate evaluation and treatment of their asthma. Due to the data contained in recent publications and the potential medical harms described in this section of this document, FDA now considers the indication “for the temporary relief of nasal congestion associated with sinusitis” inappropriate and potentially misleading in the labeled uses for OTC nasal decongestant drug products. Consumers could interpret this indication to mean that the product can be used for self-treating sinusitis. Likewise, use of the term “sinusitis” on the product’s principal display panel could cause the same misunderstanding. FDA received three comments on its proposed rule.

## **II. FDA’s Response to the Comments**

(Comment 1) One comment disagreed with the proposed rule and contended that FDA should be compelled to provide valid scientific data prior to taking the action noted in the proposed rule. The comment stated that:

- Consumers are not likely to misunderstand symptom treatment to also mean disease treatment.
- Consumers would know that they have sinusitis only after intervention by a physician.
- Consumers with recurrent sinusitis may be able to recognize the signs and be able to begin to treat the nasal congestion with an OTC nasal decongestant as they seek medical intervention.
- Consumers may be unaware that they have sinusitis and treat the associated nasal congestion with a nasal decongestant drug product, thereby allowing the sinusitis to progress in some cases.

- Because OTC nasal decongestant drug product labeling warns consumers to stop taking the medication and consult a doctor if their symptoms do not improve within 7 days or if the symptoms are accompanied by fever, consumers who follow that labeling would discontinue use of the product if they experienced fever (a symptom associated with a bacterial infection in sinusitis) or if the condition lasted more than 7 days.

- If the proposed rule is finalized, there will be no OTC labeled product that can be used for sinusitis, leaving consumers only with the option of medical intervention to begin treatment of their symptoms. This option will lead to a greater demand for antibiotics, including for episodes where not necessarily needed, which will lead to worsening of the public health due to antibiotic resistance.

- FDA has not produced data to show that  $\alpha$ -adrenergic decongestants are not appropriate for relief of nasal congestion associated with sinusitis.

- Current consumer-oriented medical information continues to note that nasal decongestants are recommended by physicians for nasal congestion associated with sinusitis. As examples, the comment cited the following information:

1. The American Academy of Otolaryngology-Head and Neck Surgery (AAOHNHNS) notes that oral and topical nasal decongestants may be used to alleviate nasal congestion associated with sinusitis.
2. The National Institute of Allergy and Infectious Diseases (NIAID) (National Institutes of Health, U.S. Department of Health and Human Services) notes that physicians may recommend decongestants to reduce congestion.
3. The American Academy of Allergy, Asthma & Immunology (AAAAI) notes that in addition to prescribing an antibiotic to control the bacterial

infection, physicians may prescribe a decongestant to reduce blockage.

- The current labeling for these products does not delay consumers from seeking appropriate treatment for sinusitis.

(Comments 2 and 3) A second comment from the AAAAI agreed with FDA's proposal to delete reference to sinusitis in the labeling of OTC nasal decongestant drug products and stated that the proposal is reasonable, appropriate, and a step in the right direction. A third comment, from a consumer, fully agreed with removal of "sinusitis" from the product labeling. The person who submitted the comment considered himself to be an average consumer of OTC drug products who contracts sinusitis at least twice a year and stated that:

- The main argument in support of the proposal is evidence that these drugs are lacking when they are recommended or prescribed for adjunctive therapy for sinusitis.

- Evidence suggests that OTC drugs may have negative effects on the treatment of sinusitis and can worsen the condition.

- Such labeling is almost a form of false advertising, that the indications are misleading, and that consumers should not be led to believe such labeling is acceptable.

- If consumers use OTC drugs to self-treat sinusitis and the condition is not properly treated, the condition could worsen dramatically, with consumers having the risk of becoming clinically worse and/or developing further complications.

- FDA is correct in its removal of the "sinusitis" language to ensure that the probability of consumers using OTC drugs for self-treatment of sinusitis will be reduced.

FDA disagrees with the comment opposing the proposed rule. FDA initially affirmed the recommendation by the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products in its advance notice of proposed rulemaking (48 FR 38312, September 9, 1976) to include the “sinusitis” term in OTC nasal decongestant drug product labeling. However, due to the data in recent publications and the potential harms described in this document, FDA no longer considers sinusitis an appropriate OTC indication and believes that the current labeling is potentially misleading to consumers. Appropriate care of sinusitis requires the attention of a health care practitioner. FDA is concerned that consumers may interpret current product labeling as implying that a nasal decongestant can treat sinusitis and will delay consulting a physician for treatment.

The comment that disagreed with the proposed rule referred to current consumer-oriented information. The comment stated that this information continues to note that nasal decongestants are recommended by physicians for nasal congestion associated with sinusitis. For example,

- NIAID notes that physicians may recommend decongestants to reduce congestion.
- AAAAI notes that physicians may prescribe a medication such as a decongestant to reduce blockage in addition to prescribing an antibiotic to control the bacterial infection.

These references clearly indicate that use of decongestants and/or adjunct therapy is at the discretion of a physician. It should also be noted that AAAAI submitted a comment agreeing with FDA’s proposal.

The comment that disagreed with the proposed rule implies that a consumer who uses an OTC nasal decongestant drug product will not delay

seeking medical attention for sinusitis because the OTC nasal decongestant drug product labeling warns consumers to consult a doctor if their symptoms do not improve within 7 days or are accompanied by fever. However, the presence of fever in consumers with sinusitis is variable (Ref. 2), and decongestant products may be combined with an analgesic that can mask these symptoms. No data were submitted to support the contention that consumers are not likely to misunderstand symptom treatment to also mean disease treatment. Neither were data submitted to support the contention that current labeling does not delay consumers from seeking appropriate treatment for sinusitis. FDA agrees with comments that state that diagnosis and definitive treatment of sinusitis requires intervention by a physician, and that consumers who are unaware that they have sinusitis may allow the condition to progress. Although FDA is not aware of data supporting the use of  $\alpha$ -adrenergic decongestants in sinusitis, FDA recognizes that physicians may advocate their use. This advocacy does not, however, make sinusitis an OTC indication. FDA concludes that the term “sinusitis” should be removed from OTC nasal decongestant drug product labeling.

### **III. FDA’s Final Conclusions**

FDA is finalizing its proposal by removing § 341.80(b)(1)(iii) (21 CFR 341.80(b)(1)(iii)) from the FM for OTC nasal decongestant drug products. FDA is also including “sinusitis” and “associated with sinusitis” as nonmonograph conditions in new § 310.545(a)(6)(ii)(C) (21 CFR 310.545(a)(6)(ii)(C)).

In addition, FDA is entering technical changes by substituting “nasal congestion” for “sinusitis” in the paragraph headings of §§ 341.85(b)(2) and (b)(3) (21 CFR 341.85(b)(2) and (b)(3)), and by removing the term “and/or (b)(1)(iii)” from § 341.85(b)(2)(ii).

Twenty-four months after the date of publication in the **Federal Register**, for products with sales less than \$25,000, and 18 months after the date of publication in the **Federal Register**, for all other products, no OTC drug product that is subject to this final rule and that contains a nonmonograph condition may be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of a new drug application (NDA) or abbreviated new drug application (ANDA). Further, any OTC drug product subject to this final rule that is repackaged or relabeled after the compliance dates of the final rule must be in compliance with the FM regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily as soon as possible.

#### **IV. Analysis of Impacts**

FDA has examined the impacts of this final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, if a rule has a significant impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of the rule on small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement of anticipated costs and benefits before



proposing “any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year.”

FDA believes that this final rule is consistent with the principles set out in Executive Order 12866 and in these two statutes. FDA has determined that the rule is not a significant regulatory action as defined by the Executive order and so is not subject to review under the Executive order. As discussed later in this section of the document, FDA concludes that the rule will not have a significant economic impact on a substantial number of small entities. The Unfunded Mandates Reform Act of 1995 does not require FDA to prepare a statement of costs and benefits for this final rule, because the final rule is not expected to result in any 1-year expenditure that would exceed \$100 million adjusted for inflation. The current threshold after adjustment for inflation is \$115 million, using the most current (2003) Implicit Price Deflator for the Gross Domestic Product.

The purpose of this final rule is to remove a labeling claim for OTC nasal decongestant drug products. Removal of this claim should reduce possible misuse and improve consumers’ self-use of these products. FDA does not anticipate that removal of this claim will significantly affect OTC sales of these products.

The final rule requires relabeling of some OTC nasal decongestant drug products, i.e., those products that currently have a claim for sinusitis in their labeling. FDA’s drug listing system identifies about 1,121 manufacturers and 381 marketers of approximately 1,960 stockkeeping units (SKUs) (individual products, packages, and sizes) of OTC nasal decongestant drug products. These

numbers include some products marketed under an NDA or ANDA. In addition, there may be a few additional marketers and products that are not identified in the sources FDA reviewed. FDA is using 2,000 SKUs as an approximate number of products in the marketplace that would be affected by this final rule.

FDA randomly reviewed the labeling of some of these nasal decongestant drug products and found that 74 of 100 products did not have a sinusitis claim. Extrapolating these numbers to approximately 2,000 SKUs of these products, FDA estimates that approximately 520 products (26 percent) would have to be relabeled. FDA estimates (based on information provided by OTC drug manufacturers) that the final rule would impose total one-time compliance costs on industry for relabeling of about \$3,000 to \$4,000 per SKU, for a total cost for 520 SKUs of \$1,560,000 to \$2,080,000.

FDA believes the actual cost could be lower for several reasons. First, as FDA explained in the final rule for OTC drug product labeling requirements (64 FR 13254 at 13280, March 17, 1999), most of the labeling changes will be made by private label small manufacturers that tend to use simpler and less expensive labeling. Second, FDA is allowing a period of 18 months (24 months for products with annual sales less than \$25,000) after publication of a final rule for manufacturers to implement the new labeling. Thus, manufacturers should be able to use up existing labeling stocks and to make the labeling changes in the normal course of business. Further, manufacturers will not incur any expenses determining how to state the product's labeling because the final rule provides that information. The final rule does not require any new reporting and recordkeeping activities. Therefore, no additional professional skills would be needed.

FDA considered, but rejected several labeling alternatives: (1) A shorter or longer implementation period, and (2) an exemption from coverage for small entities. While FDA believes that consumers would benefit from having this new labeling in place as soon as possible, FDA also acknowledges that a shorter implementation period could significantly increase the compliance costs and these costs could be passed through to consumers. A longer time period would unnecessarily delay the benefit of new labeling to consumers who self-medicate with these drug products. FDA rejects an exemption for small entities because the new labeling information is also needed by consumers who purchase products marketed by those entities. However, a longer compliance date (24 months) is being provided for products with annual sales less than \$25,000.

OTC nasal decongestant drug products are not the sole products produced by manufacturers affected by this rule. FDA believes the incremental costs of this rule will be less than 1 percent of any manufacturer's total sales. Thus, this economic analysis, together with other relevant sections of this document, serves as FDA's final regulatory flexibility analysis, as required under the Regulatory Flexibility Act.

## **V. Paperwork Reduction Act of 1995**

FDA concludes that the labeling requirement in this document is not subject to review by the Office of Management and Budget because it does not constitute a "collection of information" under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). Rather, the removal of a labeling claim is a "public disclosure of information originally supplied by the Federal government to the recipient for the purpose of disclosure to the public" (5 CFR 1320.3(c)(2)).

## VI. Environmental Impact

FDA has determined under 21 CFR 25.31(a) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

## VII. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, FDA concludes that the rule does not contain policies that have federalism implications as defined in the Executive order, and consequently, a federalism summary impact statement is not required.

## VIII. References

The following references are on display in the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Parameters for the Diagnosis and Management of Sinusitis, supplement to *The Journal of Allergy and Clinical Immunology*, 102 (6 Part 2): S107–S144, December 1998.

2. American Academy of Pediatrics Subcommittee on Management of Sinusitis and Committee on Quality Improvement, “Clinical Practice Guideline: Management of Sinusitis,” *Pediatrics*, 108(3): 798–808, 2001.

3. “Report of the Rhinosinusitis Task Force Committee Meeting,” *Otolaryngology-Head and Neck Surgery*, 117 (3 Part 2): S1–S68, 1997.

## List of Subjects

### *21 CFR Part 310*

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

### *21 CFR Part 341*

Labeling, Over-the-counter drugs.

■ Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 310 and 341 are amended as follows:

## **PART 310—NEW DRUGS**

■ 1. The authority citation for 21 CFR part 310 continues to read as follows:

**Authority:** 21 U.S.C. 321, 331, 351, 352, 353, 355, 360b–360f, 360j, 361(a), 371, 374, 375, 379e; 42 U.S.C. 216, 241, 242(a), 262, 263b–263n.

■ 2. Section 310.545 is amended by adding paragraph (a)(6)(ii)(C) to read as follows:

**§ 310.545 Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses.**

(a) \* \* \*

(6) \* \* \*

(ii) \* \* \*

(C) Approved as of [*insert date 18 months after date of publication in the Federal Register*]; [*insert date 24 months after date of publication in the Federal Register*], for products with annual sales less than \$25,000. Any

ingredient(s) labeled with claims or directions for use for sinusitis or for relief of nasal congestion associated with sinusitis.

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## **PART 341—COLD, COUGH, ALLERGY, BRONCHODILATOR, AND ANTIASTHMATIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE**

- 3. The authority citation for 21 CFR part 341 continues to read as follows:

**Authority:** 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

- 4. Section 341.80 is amended by removing paragraph (b)(1)(iii),

- 5. Section 341.85 is amended by revising the headings in paragraphs (b)(2) and (b)(3) and by revising paragraph (b)(2)(ii) to read as follows:

### **§ 341.85 Labeling of permitted combinations of active ingredients.**

\* \* \* \* \*

(b)(2) *For permitted combinations containing an analgesic-antipyretic active ingredient identified in § 341.40(a), (c), (f), (g), (m), (q), and (r) when labeled for relief of hay fever/allergic rhinitis and/or nasal congestion symptoms.*

\* \* \* \* \*

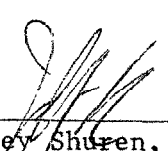
(ii) The indication(s) for the cough-cold ingredient(s) consists of the labeling for antihistamines in § 341.72(b)(1) or (b)(2) and/or nasal decongestants in § 341.80(b)(1)(ii), as appropriate, and the labeling for any other cough-cold combination. This labeling may follow a separate bullet(s) or may be combined with the indication in paragraph (b)(2)(i) of this section.

(b)(3) *For permitted combinations containing an oral analgesic-antipyretic active ingredient identified in § 341.40(a), (c), (f), (g), (m), (q), and (r) when*

*labeled for relief of general cough-cold symptoms and/or the common cold and  
for relief of hay fever/allergic rhinitis and/or nasal congestion symptoms.*

\* \* \* \* \*

Dated: 9/26/05  
September 26, 2005.

  
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Jeffrey Shuren,  
Assistant Commissioner for Policy.

[FR Doc. 05-????? Filed ??-??-05; 8:45 am]

**BILLING CODE 4160-01-S**

